L-Dopa Therapy in Parkinson's Disease:

A Critical Review of Nine Years' Experience

SUMMARY.—The last 10 years have seen great activity in the investigation of cerebral catecholamines, particular attention having been paid to dopamine. The low dopamine content in the basal ganglia and in the urine of patients with Parkinson's disease led to the logical use of the precursor DOPA in the treatment of this disorder. Between 1961 and 1966, both the oral and the intravenous routes were utilized and some effects were noted upon akinesia and rigidity. The doses then used were low and the results remained somewhat controversial. When higher oral levels of L-dopa were introduced, the beneficial action of L-dopa upon parkinsonian symptoms and signs was proved beyond doubt, but there came to light a number of troublesome side effects, the worst of which were hypotension and a variety of abnormal involuntary movements. Recently, new approaches to the therapy have been tried and the sum total of these observations is to challenge our peace of mind regarding a seemingly logical chain of events. We are convinced that such second thoughts will eventually result in better and safer methods of treating this too frequent and disabling neurological disorder.

When James Parkinson described paralysis agitans in 1817, little did he suspect that it would take 150 years for an effective treatment to be found. It is the story of that therapeutic approach which will be detailed in the present paper. As recently as 1958 it could be said during the first of many symposia on Parkinson's disease: "In our opinion the successful surgical intervention is far more impressive than any medical degrees of improvement."[1] This statement was based upon the results with standard anticholinergic and antihistaminic drugs and was found by Duvoisin[2] to be equally applicable in 1965. However, clinical and biochemical studies reported during the last 12 years make the present situation very different.

The abnormal metabolism of catecholamines in Parkinson's disease demonstrated simultaneously in 1960 by workers in Austria[3] and in Canada[4-6] was the consequence of earlier postulates and investigations by Carlsson and his co-workers[7, 8] and by Everett and Toman,[9] and led to the trial of dopamine precursors in this condition.[10, 11] This approach has received a large amount of experimental and clinical support and could be said to be "rational". However, some of the basic tenets underlying the apparently logical sequence of events may have been challenged by more recent experiments. It therefore seems appropriate to review the present state of knowledge in this field in the light of our own experience gained from human and animal experiments over the last nine years.

RATIONALE FOR THE USE OF L-DOPA IN PARKINSON'S DISEASE

For a number of years it had been known that reserpine can produce a parkinsonian syndrome. The reason for this became clearer when Bertler and Rosengren[12] and Sano *et al.*[13] demonstrated that noradrenaline had a characteristic distribution within the brain different from that of its precursor dopamine. The latter was found mainly in the basal ganglia and substantia nigra while the former was in greatest concentration in the hypothalamus and brain stem. The brain could be depleted of both by reserpine. This difference in localization, as well as some divergent peripheral effects,[14] led to the postulate that dopamine could have independent physiological functions in the brain and even at the periphery. The evidence for this conclusion, and for the existence of specific dopamine receptors, has been thoroughly reviewed by many authors[15-20] and will not be repeated here, except in summary (Table I). Such overwhelming arguments in favour of a significant role for dopamine in the functioning of the extrapyramidal centres are strengthened by pharmacological experiments in animals and by observations in human parkinsonism:

(a) *Pharmacology of dopamine in animals*

Reserpine and benzoquinolizine derivatives mobilize monoamines, decrease their cerebral concentrations, particularly that of dopamine,[7, 41-43] and produce extrapyramidal syndromes.

L-dopa suppresses or decreases the extrapyramidal effects of reserpine and benzoquinolizine derivatives in animals[44] and man.[45, 46] This effect is most likely to be due to repletion of dopamine, since direct noradrenaline replacement through 3,4-dihydroxyphenylserine is not successful.[52]

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TABLE I.—Role of Dopamine in Basal Ganglia
Summary of Evidence

A. DISTRIBUTION

Presence in brain of dopamine.[21-23]
80% of brain dopamine in corpus striatum.[13]
Presence of dopamine in other extrapyramidal areas: pallidum, substantia nigra.[7]
In striatum, tyrosine is converted mainly to dopamine[24] with little further transformation to noradrenaline as in other areas of brain,[25] despite ample supply of dopamine-β-hydroxylase,[26] dopamine and the enzyme being possibly situated in different compartments.[20]

B. BIOCHEMISTRY

Presence in basal ganglia of all enzymes necessary for dopamine synthesis and metabolism: decarboxylase, dopamine-β-hydroxylase, monoamine-oxidase, catechol-O-methyl transferase.[26, 27]
Presence in basal ganglia and substantia nigra of metabolic products of dopamine: methoxytyramine, homovanillic acid (HVA).[28, 30]

C. HISTOCHEMISTRY

Demonstration and mapping out of a nigrostriatal dopaminergic pathway with fluorescent methods[31] and with modified silver methods (Moore, R. W., unpublished).
Presence of dopamine-containing nerve cells in substantia nigra, but virtually none in striatum.[32]
Presence of dopamine-containing nerve terminals of fine calibre in the striatum[33] organized into a closely packed, dense meshwork.

D. NEUROPHYSIOLOGY

Most workers agree that dopamine has an inhibitory effect on the activity of single neurons in the brain, both in lower animals and in mammals.[15]
Stimulation of the substantia nigra and centrum medianum of thalamus liberates dopamine in the striatum.[34, 38]
Lesions in the substantia nigra in rats[31] and in monkeys[35] produce a decrease in dopamine concentration in the ipsilateral striatum as well as a decrease in tyrosine hydroxylase and dopa-decarboxylase[36, 37] in the same nuclei.
There is evidence of specific dopamine receptors in the brain[39] and in the kidneys.[40]

TABLE II.—Biochemistry of Parkinson's Disease

A. BRAIN

Decreased dopamine content in basal ganglia,[3, 15, 55, 56] more evident on one side in hemiparkinsonism[57] and correlated with the severity of damage to the substantia nigra.[59]
Decrease in dopamine content of substantia nigra.[60]
Decreased serotonin content in brain.[58]
Decrease in the concentration of homovanillic acid (HVA) in the striatum and substantia nigra.[61, 62]
Decreased noradrenaline content in the hypothalamus.[3, 65]
Normal activity of monoamine oxidase and substance P in striatum.[63] Activity of dopa-decarboxylase reported normal[64] or decreased[65] in basal ganglia and thalamus.

B. CEREBROSPINAL FLUID

Decrease in HVA in CSF of idiopathic and post-encephalitic parkinsonians.[66-68]
Abnormal pattern of CSF amino-acids[118] with apparent increase in glycine and decrease in tyrosine concentrations.
Decreases in HVA are also present in other entities: epilepsy,[119] presenile and senile dementias.[101]

C. BLOOD

Normal values of serum tyrosine[120] and phenylalanine.[121]
Abnormal glycine concentration.[118]

D. URINE

Decrease in total and in free urinary dopamine in post-encephalitic parkinsonism.[6, 18, 19, 65, 69, 70-72]
Less evident decrease in total urinary dopamine in idiopathic Parkinson's disease[6, 72, 73] particularly if dystonic or hyperkinetic symptoms are present.[74] With advancing akinesia[19] the dopamine content decreases.
Usually normal values of urinary homovanillic acid[72, 75, 76] except in far advanced akinetic cases where it is decreased.[77]
Normal values of urinary adrenaline, noradrenaline and vanylmandelic acid (VMA).[6, 76, 78]
Increased turnover rate of tritiated dopamine to HVA.[79]
Decreased or normal urinary values of 5-HIAA.[18, 72, 80, 81]
Increase in urinary excretion of a compound with a chromatographic behaviour similar to 3,4-dimethoxyphenylethylamine.[122] Thought by some to be tryptamine,[123] by others p-tyramine[124] and by still others metabolic products of drugs.[119]

Everett and Wiegand[53] in studies carried out from 1958 to 1962 clearly demonstrated not only that L-dopa corrected some of the extrapyramidal effects of reserpine, but that there was also a correlation between the level of brain catecholamines (particularly dopamine) and increasing degrees of motor behaviour and aggressiveness in mice. Seiden and Hanson[54] also demonstrated the effect of L-dopa on reserpine-induced changes in conditioned avoidance responses.

Butyrophenones and phenothiazines provoke extrapyramidal syndromes, and are known to interfere with dopamine receptors and to act as competitive inhibitors of the catecholamine membrane pump.[39, 47-51]

In all cases (reserpine, butyrophenones, phenothiazines) it would appear that either receptor blockade or re-uptake blockade triggers a compensatory feedback mechanism, increasing transmitter synthesis and, consequently, dopamine turnover within the basal ganglia.

(b) *Pharmacology of dopamine in man*

The correlation between some modification of dopamine metabolism and extrapyramidal symptomatology is thus clearly established in animals. Studies of Parkinson's disease in humans reinforce this conclusion and are summarized in Table II.

DOPA IN HUMANS

Dopa (3,4-dihydroxyphenylalanine) was first synthesized in 1911 by Casimir Funk, and its L-form was identified in Vicia faba beans in 1913 by Guggenheim, who also was able to demonstrate on himself its emetic action.[15] Following the demonstration by Carlsson *et al.*[44] in 1956 of the depleting effect of reserpine upon catecholamines, the same group was able to show that L-dopa can serve as a reserpine antagonist[42] and abolish some of the extra-pyramidal effects produced by this drug. The identification of dopamine as a component of human brain by Montagu[23] in 1957 and the further localization of the high concentration of dopamine in the basal ganglia[7] led to the first trial of L-dopa in humans by Degkwitz and collaborators[45] in 1960. This was followed by a study in drug-induced extra-pyramidal disorders by McGeer and collaborators[84] in 1961, with negative results.

In 1961, simultaneously and independently, two groups reported on the use of L-dopa in Parkinson's disease. In Montreal, Barbeau and collaborators[10, 82] using oral L-dopa, noticed marked but short-lasting improvement in rigidity and tremor, while in Vienna, Birkmayer and Hornykiewicz[11] used the intravenous route and observed changes in akinesia.

L-DOPA IN PARKINSON'S DISEASE

Following these initial reports a great number of papers, reporting conflicting results and with a wide variety of approaches, were published. It is sometimes difficult to follow clearly the trend in these early years, except to note that almost every dosage schedule, route

TABLE III.—Early Trials with L-DOPA in Parkinson's Disease

A. Oral

(1) FAVOURABLE REPORTS

1. Barbeau (1961) (1962) (1962) (1968) (1969)
2. Birkmayer (1962) (1964) (1967)
3. Sourkes (1963)
4. Brück (1965)
5. Bernheimer (1966) (1966)
6. Tzavellas (1966)
7. Travenec (1966)
8. Bruno (1966)
9. Oehme (1966)

(2) MIXED OR UNFAVOURABLE REPORTS

1. Greer (1963)
2. McGeer (1964)
3. Rinaldi (1965)

B. Intravenous

(1) FAVOURABLE REPORTS

1. Birkmayer (1961) (1962) (1964) (1967)
2. Gerstenbrand (1962) (1963) (1965)
3. Hornykiewycz (1962) (1966)
4. Friedhoff (1963)
5. Hirschmann (1964)
6. Umback (1964) (1965) (1966) (1967)
7. Brück (1965)
8. Diemath (1965)
9. Tzavellas (1966)
10. Travenec (1966)
11. Oelssner (1967)
12. Voller (1968)
13. Fasano (1969)
14. Bettag (1969)

(2) MIXED OR UNFAVOURABLE REPORTS

1. Rinaldi (1965)
2. Metzel (1965)
3. Brigida (1965)
4. Duvoisin (1965)
5. Pazzagli (1966)
6. Aebert (1967) (1967)

(3) NEGATIVE RESULTS (double-blind procedure)

1. Fehling (1966)
2. Rinne (1968)

TABLE IV.—Early Trials with DOPA in Parkinson's Disease

LESSONS AND CONCLUSIONS AS OF JUNE 1966

Dopa effective against *rigidity* and mainly *akinesia.*

L-dopa preferable to D, L-dopa.

D-dopa ineffective.

Dopa probably acts through transformation into dopamine *in the brain.*

Injections or infusions are useful, but difficult for long-term treatment.

Side effects: nausea, loss of appetite, hypotension.

Combination with amphetamine, propylhexedrine, monoamine-oxidase inhibitors or surgery useful.

Cost still prohibitive for long-term treatment.

TABLE V.—Recent Reports of Trials with L-DOPA in Parkinson's Disease

(All with high doses *per os*)

1. COTZIAS, G. C., Van WOERT, M. H. and SCHIFFER, L. M.: *New Eng. J. Med.*, 276: 374, 1967.
2. COTZIAS, G. C. AND PAPAVASILIOU, P. S.: Therapeutic studies of parkinsonian patients; long term effects of DL-DOPA and L-DOPA. *In:* Second International Congress of Neuro-Genetics and Neuro-Ophthalmology of the World Federation of Neurology, Montreal, September 17-22, 1967, Excerpta Medica International Congress Series No. 154, Amsterdam, 1967, p. 30 (abstract).
3. COTZIAS, G. C. *et al.: Trans. Ass. Amer. Physicians,* 81: 171, 1968.
4. YAHR, M. D. *et al.: Trans. Amer. Neurol. Ass.*, 93: 56, 1968.
5. COTZIAS, G. C. *et al.:* Long-term effects of dopa on parkinsonism: a proposal. *In:* Third symposium on Parkinson's disease, edited by F. J. Gillingham and I. M. Donaldson, E. & S. Livingstone Ltd., Edinburgh, 1969, p. 178.
6. DUVOISIN, R. *et al.:* The use of L-dopa in parkinsonism. *In:* Third symposium on Parkinson's disease, edited by F. J. Gillingham and I. M. Donaldson, E. & S. Livingstone Ltd., Edinburgh, 1969, p. 185.
7. BARBEAU, A.: *Un. Méd. Canada*, 98: 183, 1969.
8. COTZIAS, G. C., PAPAVASILIOU, P. S. AND GELLENE, R.: *New Eng. J. Med.*, 280: 337, 1969.
9. BOSHES, B. AND BRUMLICK, J.: *Illinois Med. J.*, 135: 253, 1969.
10. WYCIS, H. T. *et al.:* The value of L-dopa in surgical treatment of Parkinson's disease. Paper presented at the annual meeting of the Harvey Cushing Society, Cleveland, April 13-18, 1969. Unpublished.
11. STELLAR, S. *et al.:* A study of L-dopa and thalamic surgery in the treatment of parkinsonism. *Ibid.*
12. CALNE, D. B. *et al.: Lancet*, 1: 744, 1969.
13. REFSUM, S.: *Nord. Med.*, 81: 570, 1969.
14. TISSOT, R. *et al.: Presse Méd.*, 77: 619, 1969.
15. GODWIN-AUSTEN, R. B. *et al.: Lancet*, 2: 165, 1969.
16. YAHR, M. D. *et al.:* Paper presented at the meeting of the New York Academy of Medicine, June 1969. Unpublished.
17. McDOWELL, F. M.: *Ibid.*
18. COTZIAS, G. C., PAPAVASILIOU, P. S. AND MENA, I.: Parkinsonism, dopa and chronic manganese poisoning. *In:* The Fourth International Congress of Neurobiological Surgery, and the Ninth International Congress of Neurology, New York, September 20-27, 1969, Excerpta Medica International Congress Series No. 193, Amsterdam, 1969, p. 169 (abstract).
19. DUVOISIN, R. *et al.:* The present status of L-dopa in the treatment of parkinsonism. *Ibid.*, p. 170 (abstract).
20. TIMBERLAKE, W. H., ZIEPER, I. AND SCHWAB, R. S.: Double-blind study of L-dopa treatment of parkinsonism. *Ibid.*, p. 170 (abstract).
21. McDOWELL, F. *et al.:* The treatment of Parkinson's disease with dihydroxyphenylalanine. *Ibid.*, p. 170 (abstract).
22. BARBEAU, A. AND GILLO-JOFFROY, L.: Treatment of Parkinson's disease with L-dopa and Ro 4-4602. *Ibid.*, p. 171 (abstract).
23. SIEGFRIED, J. *et al.:* The treatment of Parkinson's disease with L-dopa combined with a decarboxylase inhibitor. *Ibid.*, p. 171 (abstract).
24. STEG, G.: Side-effects during treatment with L-dopa in parkinsonism. *Ibid.*, p. 171 (abstract).
25. SPIEGEL, E. A. *et al.:* Restoration of speed in parkinsonian and experimental brady- and akinesia. *Ibid.*, p. 169 (abstract).
26. SCHWAB, R. S.: L-dopa vs surgery in Parkinson's disease. *Ibid.*, p. 172 (abstract).

of administration and combination of drugs were used.[83] We have tried to summarize these papers according to types of results and list them in Table III under the name of the first author and year of publication.

Most of the initial reports were favourable, whether the drug was given by the oral route or through slow intravenous infusions, generally in combination with a monoamine-oxidase inhibitor, amphetamines or surgical management. The need for repeated injections two to three times a week made this approach difficult, and soon a number of reports appeared questioning the existence of the so-called "dopa-effect". Successively Rinaldi, Margherita and De Divitus,[85] Duvoisin,[2] Fehling[86] and Rinne and Sonninen[72] concluded that the changes observed were barely more than a placebo response.

Our own experience from 1960 to 1968 was with oral L-dopa given in doses of between 300 and 2000 mg. per day to a total of 43 patients. Because of cost limitations

the patients never received the drug for more than a few days at a time. Two of the first patients were given 300 mg. daily over a period of three months.[10] In 34 of these patients a favourable effect from L-dopa administration was observed and measured. The duration of its maximum effect varied between two to four hours (for a single dose) and three to four days after cessation of L-dopa at 300-600 mg./day. The improvement was mainly in rigidity and tremor.

In the summer of 1966, despite some trials with occasional high doses of oral D,L-dopa by a few authors, the general impression was that dopa had definite effects on the symptoms of rigidity and akinesia, but that its therapeutic usefulness was still to be demonstrated. The lessons and conclusions that prevailed at that time were summarized by us in a lecture in June 1966 and are listed in Table IV.

In August 1966, at the Brookhaven National Laboratories, Cotzias and his co-workers had the courage to increase the dose of oral D,L-dopa gradually to levels between 3 and 16 g. per day. In 1967 they reported on 16 parkinsonian patients so treated, with "a striking sustained improvement in several patients".[87] Major side effects, particularly hematologic complications, developed in some patients and presented a problem in continuation of therapy. Shortly afterwards, at the Second International Congress of Neuro-Genetics in Montreal,[88] the same authors indicated that they were then using L-dopa on 12 patients, five of whom had participated in the earlier trial with D,L-dopa. Again the preliminary evidence was that "continuous oral administration of L-dopa may bring sustained relief to some parkinsonian patients, lasting for the several months of the trial practised thus far". The results were graphically illustrated on films. Following this striking demonstration, a number of studies were initiated, first in New York, then in Montreal, Boston and Chicago. The conclusions of the first of these studies were given in June 1968 by Yahr and collaborators[89] at the annual meeting of the American Neurological Association. They confirmed in every way the previous studies of many authors since 1961 and the more evident results of the Cotzias approach with high doses of L-dopa. Since June 1968, L-dopa has been the subject of literally hundreds of clinical trials. Some of the earliest, already reported, are listed in Table V. As of November 1969, more than 2000 patients have been treated with L-dopa, under a variety of protocol supplied by participating pharmaceutical houses or, unfortunately, left to the whims and fancy of the individual clinicians. In general the results are in complete agreement as to overall improvement, incidence of side effects and limitations. Double-blind placebo studies, carried out in particular by Yahr *et al.*[89] and by Timberlake, Zieper and Schwab[90] offer similar encouraging results.

TABLE VI.—Results of L-DOPA in Parkinson's Disease
Total Number: 80 Patients

Objective range of functional improvement (after two months of treatment)		*No. of patients*	%
80—100%	(Very good)	9	11.2
50— 79%	(Good)	54	67.5
20— 49%	(Moderate)	9	11.2
0— 20%	(Poor)	8	10.0

PERSONAL RESULTS

Since 1968, we have treated, for periods exceeding two months, some 86 patients, with progressively higher oral doses of L-dopa, reaching a mean value of 4.3 g. per day with a maximum of 7 g.* Our detailed findings will be reported in a companion paper to be published later in this Journal. We will give only a short summary at this time because we believe these results are fairly representative of the experience of most groups.

The 86 subjects (62 men, 24 women) had a mean age of 59.7 years (range: 22-82). Eighty patients had Parkinson's disease, including 10 with a possible history of encephalitis; also included for short-term control studies were one case of dystonia musculorum deformans (aged 22), one of presenile dementia, one of senile dementia, one of Huntington's chorea, one of luetic parkinsonism and one of multiple sclerosis.

*Studies on these patients were carried out in the Hôtel-Dieu Hospital, the Clinical Research Institute of Montreal, the Jewish Convalescent Hospital and Maimonides Hospital, with the collaboration in the latter two institutions of Drs. Harold Mars, Israel Libman and Arthur Schwartz.

The average dose used in Parkinson's disease was 4.8 g. per day with a range of 1.5 to 7.0 g. This level was obtained after four to six weeks in hospital with a very slow upward titration similar to that used by Cotzias.[91] Performance of the patients was measured by a battery of tests previously described[92, 93] and the results, transposed into a total score, are expressed as percentage improvement over the baseline control period (Table VI).

Sixty-one of the 80 parkinsonian patients (79%) were improved by more than 50% in their general performance. Moderate improvement, usually manifested by modification of one or more symptoms without overall satisfactory changes, was observed in a further nine patients (11%). There were eight failures, due to side effects (two cases) or absence of objective improvement (six cases), despite maximum dosage. To these must be added the failures in the senile and presenile dementia cases, in the luetic parkinsonian patient and in one patient with multiple sclerosis, and the instances of worsening of the symptoms with relatively small doses (1-2 g. per day), viz. one case of Huntington's chorea and one of dystonia musculorum deformans. The results in our series thus correspond closely to what has been reported by Cotzias, Papavasiliou and Gellene,[94] Yahr *et al.*,[95] McDowell *et al.*[96] and others.

DISCUSSION OF RESULTS

The most important factors in obtaining significantly favourable results and in avoiding major side effects from L-dopa treatment appear to be the gradual upward titration of the oral dose as well as a program of mobilization. If these two principles are closely adhered to, as outlined many times by Cotzias, it is possible in almost all patients to reach a "plateau" dose-level of approximately 4 g. per day without complications. In our opin-

TABLE VII.—Side Effects with L-DOPA
(80 patients treated for more than two months)

Symptoms	*No. of cases*	*%*
A. CLINICAL		
Nausea and/or vomiting	35	43.7
Hypotension:		
symptomatic 9		
asymptomatic 16	25	31.2
Hypertension	1	1.2
Anorexia with loss of weight	1	1.2
Polyuria	4	5.0
Somnolence	4	5.0
Palpitations or arrhythmias	6	7.5
Confusion, hallucinations or vivid dreams	13	16.2
Depressive episodes	9	11.2
Abnormal involuntary movements	40	50.0

B. BIOCHEMICAL		
Analysis	*No. of cases*	*%*
Transient increase in BUN	15	18.7
Transient increase in uric acid (blood)	39	48.8
Transient increase in alkaline phosphatase	4	5.0
Minimal (less than 10%) decrease in total leukocyte count	3	3.7

ion this initial study, lasting from four to six weeks, should be done in hospital. At plateau level, if the drug is well tolerated and if the patient has obtained at least a 50% improvement in functional capacities as objectively measured, he can be followed up regularly on an outpatient basis. By gradually and slowly modifying the dose upward or downward, it is possible to obtain even more improvement after a further two to four months, without a recurrence of the initial annoying side effects of nausea, vomiting, loss of appetite or postural hypotension.

In our experience there has been at least partial improvement in almost all symptoms of Parkinson's disease in the majority (90%) of patients. The degree of this improvement is greater than that previously obtained by conventional anticholinergic or antihistaminic medication and in most cases is greater than the benefits obtained with stereotaxic surgery. At first, and until a dosage of nearly 2.5 g. per day is reached, the improvement is mainly subjective. The patient feels better, his mood is cheerful and he attempts to perform tasks that have been beyond him for many years. During this period the significant drawbacks are nausea, occasional vomiting and a striking loss of appetite. Most patients will tolerate the morning nausea if the dose is increased very slowly. L-dopa must never be given on an empty stomach. It is preferable to eat many small meals rather than fewer heavy ones.

After reaching a dose of 3 g. per day a significant and often sudden improvement in motor functions and in general performance occurs. The exact level where this will take place varies from patient to patient, but is almost a constant phenomenon. From that point on, it is easy to measure objective modifications of signs. The beneficial effects of L-dopa on the individual symptoms of rigidity, akinesia, tremor, sialorrhea, gait and posture, memory, mood, associated movements, speech, handwriting, oculogyric crises and even dysuria will be detailed in the companion paper. At this time it is sufficient to mention that the most striking effect appears to be upon the hypokinesia manifested by loss of associated movements and upon postural and gait impairment. Rigidity and hypokinesia can at times be completely reversed. On the other hand, tremor is more refractory. At first, and concomitant with a reduced rigidity, there may be a slight increase in the amplitude. Over the long term, however, there is a definite decrease in both amplitude and rate (to 3 per sec.) in most patients, with eventual disappearance in a few. This statement is applicable to the classical, slow (3 to 8 per sec.) postural tremor of Parkinson's disease. L-dopa does not improve cerebellar, senile or familial types of tremor; in fact, it usually increases the latter. This observation may therefore suggest a pharmacological approach to the understanding of the various tremor mechanisms.

The beneficial effects of L-dopa do not appear to be modified or limited by factors of age, severity of disease or duration of symptoms. However, the most severely affected patients, because of other factors such as arteriosclerosis or liver or kidney dysfunction, have the highest incidence of severe complications. Previous stereotaxic surgery, unless there are sequelae of pyramidal tract damage, is not a limiting factor.

Even if the improvement can be considered sustained, there is often a marked variation in individual performance from day to day or within the same day. Occasional short-lasting refractory periods varying from a few minutes to three or four hours will occur in patients who otherwise are perfectly controlled. During these episodes there is often increased restlessness, a feeling of tension or of body warmth, and excessive nasal discharge with hyperhidrosis and even pupillary dilatation. These refractory periods occur usually one to two hours after an oral dose of L-dopa and are worse after a heavy protein meal.

Similarly there may be episodes of longer duration, lasting up to a few weeks, with suboptimal performance despite maintenance of the same dosage schedule. At such times there is a marked increase in freezing and the re-emergence of tremor.

DISCUSSION OF SIDE EFFECTS

However encouraging the prospects, it must be stated that such results are not obtained without risks and complications. The incidence of side effects in our series is listed in Table VII and will be detailed in the companion paper. An analysis of these phenomena must be included, because their understanding will contribute to the eventual success of this form of therapy. At this point, however, I would like only to emphasize the following items: nausea, vomiting, hypotension, mental changes and abnormal involuntary movements.

Nausea and vomiting, usually in the morning, are seen at some stage in almost all patients, but become a clinical problem in only 40%. The slower the rate of increase, the slighter the manifestations. Vomiting has been a limiting factor of

treatment in only one of our patients, who could not tolerate even small doses of the drug.

Akinetic parkinsonian patients generally have a blood pressure 15 to 20 mm. Hg below the average for their age group. L-dopa, contrary to expectations, produced hypertension in only one patient. In 25 others we observed a fall in systolic blood pressure greater than 20 mm. Hg. This finding usually lasted three to six weeks and corresponded to the adjustment period as regards dose and mobilization. Usually the phenomenon was not symptomatic and blood pressure started to return to normal during the second or third month of therapy. In some cases a rebound, but slight, hypertension could be observed after five to six months. In nine patients, however, the low blood pressure became symptomatic when the upright posture was assumed. Light-headedness and vertigo were reported by some patients, while actual syncope with complications occurred in eight. One patient had a pulmonary embolus during the initial phase of mobilization but recovered. Three patients had acute myocardial infarcts, one while playing tennis for the first time in 15 years. Two patients had minor focal motor seizures. In one case this was proved by gamma-encephalography to be due to a small localized cerebral infarct (embolus ?). Finally, one patient suffered a cerebrovascular accident with right hemiplegia and aphasia after cutting down a large tree. Although these episodes were severe and should not be dismissed lightly, in most cases the low blood pressure could be corrected by the usual measures, particularly the wearing of elastic stockings or pants.

Personality changes occurred in a number of parkinsonians. The general mood-elevating and awakening effect of L-dopa was observed in most patients. However, this was occasionally accompanied by a false sense of omnipotence and "insouciance". The judgment of some patients in the face of major decisions was often faulty. A behaviour pattern with frontal lobe overtones was evident in some patients, especially in the sexual sphere. A clear-cut, visually evident increase in libido occurred in at least four male patients but, unfortunately, erections were not sustained and copulation was terminated with premature ejaculation. It is difficult to evaluate the presence or absence of this effect in our female patients, but we believe that it is present in them as well.

In rare cases confusion, hallucinations and clearly psychotic behaviour were present. The confusion resembled most closely a toxic delirium. Vivid dreams with sexual or paranoid features were present on occasion. In other patients, sleeplessness and agitation were the rule. Paranoid manifestations were probably the most frequent, but in all cases such tendencies had been manifested before treatment with L-dopa and thus represented exacerbations. In nine patients behaviour manifestations took the paradoxical form of a more severe depression, with suicidal ideas. This occurred mainly in patients with the less marked improvement who lacked motivation and who often had been "expecting a miracle", because of the excessive publicity given this new form of treatment in the press.

The most striking, and important, side effect is the production of abnormal involuntary movements in more than 50% of patients. This phenomenon appears to be dose-related and occurs approximately at the time of optimal performance. An important observation is that when these dyskinesias appear, tendon reflexes are weak and there now is hypotonia. Very often patients can predict the onset of these movements through a strange feeling of warmth or tingling in the part of the body eventually affected. The types of movements observed are almost as variable as the number of patients. In Table VIII we have listed most of the manifestations observed in our 80 patients with Parkinson's disease. Usually the first anomaly is in the cephalic sphere, with orofacio-buccal movements predominating. The tongue is unusually active, with slow or rapid protrusion and rotation; gnawing or chewing motions are also frequent. Abnormal involuntary movements in the limbs appear later, particularly in the hands. In fewer cases the lower limbs are also involved. When this is the case, severe athetosis, chorea-athetosis or ballismus can occur.

We will describe these phenomena in more detail in another paper because we believe they constitute the eventual major limiting factor of present L-dopa therapy. At this time, suffice it to say that they occurred in 50% of our parkinsonian patients, but could certainly be found in almost 100% if the level of L-dopa was pushed sufficiently high. To date they have been reversible upon reducing the dose of the drug, but in some cases after a few months they have tended to recur at progressively lower doses. In one patient they appeared first at 6.5 g. per day and are now found, still with satisfactory reduction of rigidity and akinesia, at a level of 1.5 g. per day. At first these movements, particularly if they are limited to the face, are not noticed by the patient himself. They become bothersome mainly when they affect the limbs or when the peculiar wave-like nodding of the head becomes severe. Although most authors talk about chorea, dystonia or tics, it is our opinion that these dyskinesias differ markedly from what occurs in natural disorders of the basal ganglia. In some ways they resemble the dyskinesias seen during the acute phase of von Economo's encephalitis or with some phenothiazines. The cephalic phenomena are very similar to the so-called "tardive dyskinesias" of drug therapy, but the latter usually do not manifest themselves by the severe limb movements seen while the patient is receiving L-dopa. Small doses of phenothiazines (Stelazine) or pyridoxine can reduce some of these side effects. Unfortunately, as the drugs improve the dyskinesias, they adversely affect the parkinsonian state. This observation is of importance in view of the common habit of prescribing proprietary vitamins for chronically ill patients. Even the small amounts of pyridoxine found in most such preparations will eventually be sufficient to combat the effect of L-dopa.

An interesting observation can now be reported. In none of our four non-parkinsonian patients, even when taking comparable levels of L-dopa for identical periods, did we observe the slightest indication of dyskinesia. This was particularly evident in the patient with multiple

TABLE VIII.—DOPA-Induced Dyskinesias

1. CEPHALIC DYSKINESIAS

(a) *Ophthalmic:*
Pseudo exophthalmos: "wide-eyed" or astonished expression, with lifting of eyebrows.
Episodes of rapid blinking.
Sudden blepharospasms as if in intense concentration and often with hand gestures.
Sudden lateral deviations of eyes with or without rotation of head.
Short-duration internal strabismus with blurring of vision.
Intermittent mydriasis.

(b) *Facial:*
Unilateral rictus with or without short-duration hemifacial spasm.
Trismus.
Asymmetrical choreic or myoclonic movements of face (cheeks).

(c) *Oro-bucco-lingual:*
Rapid, short-duration protrusion of the tip of the tongue.
More prolonged protrusion with rhythmic and rolling movements of the tongue and licking motions.
Clicking and smacking of lips and tongue with or without gnawing.
Lateral or rotatory movements of lips and chin, sometimes like chewing, sometimes like rumination.
Rhythmic clicking of dentures (from tongue, cheek and jaw movements).
Rare palatal myoclonus.
Vocalization changes (nasal voice, slurring) with marked tongue movements.

(d) *Cervical:*
Latissimi contractions (with trismus).
Slow wave-like, anteroposterior rocking or nodding of the head.
Much rarer lateral tremor of the head (similar to senile tremor).
Torsion dystonia (torticollis).
Short synchronous bilateral "shrugging" movements of shoulders.
Sudden massive unilateral contractions of shoulder muscles with bending of the head laterally towards the raised shoulder.

2. TRUNCAL DYSKINESIAS

(a) *Respiratory:*
Hyperventilation, "air hunger" dyspnea, with panting.
Myoclonic jerks of diaphragm and intercostal muscles.

(b) *Postural:*
Whole body rocking when sitting.
Oscillations ("swaying in the breeze") while standing.
Oscillatory movements of the pelvis ("belly-dancing").
Compensatory lateral flexion (scoliosis), either occasional or constant and progressive.
Opisthotonic posture.
Acute akathisia anxiety reactions with inability to stay in one spot.

3. UPPER EXTREMITY DYSKINESIAS

(a) *Proximal:*
Slow wing-like flapping of entire arm, with elbow moving most.
Internal rotation with extension and retroversion of arm.
True ballistic movements ("arm shoots out").
Slow reptilian motion of arm with extension of hand and fingers alternating with flexion (athetosis).

(b) *Distal:*
Rapid jerking movements of fingers with or without extension and spreading.
Restlessness of hands and increased gesticulation ("latinization").
Saccadic (3 per sec.) lateral movement of whole hand from the wrist.
Tremor modification: increase in amplitude in initial phase of treatment (with diminishing rigidity) followed by decrease in rate and amplitude.

4. LOWER EXTREMITY DYSKINESIAS

(a) *When lying down:*
Extension spasms of legs (kicking).
Restlessness (akathisia).

(b) *When sitting:*
Balancing motion of the leg from the knee: movement like organ player (lateral) or shuffling (back and forth) or mixture of both types.
Lateral oscillations of knee or ankle.
Rocking motion of foot resting on floor: alternate lifting of toes or heel.
Rhythmic spreading of toes.

(c) *When standing:*
Constant shifting from one foot to the other (akathisia).

(d) *When walking:*
Internal rotation of ankle progressing to whole limb internal rotation and circumvolution.
Slow wave-like motion of foot (athetosis).
More rapid, sudden, propulsion of whole limb (ballismus).

sclerosis who received up to 7 g. per day. Cotzias and his colleagues[94] have reported the same finding in manganese miners and in two normal controls after at least six months' administration of the drug. Bunney *et al.*[97] observed no abnormal movements in a case of depression after 106 days on 7 g. per day of L-dopa. In our series dyskinesias already present were made worse, in one patient with dystonia musculorum deformans and in one with Huntington's chorea.

In conclusion, I would like to mention some unusual, but not necessarily uncommon, side effects of L-dopa therapy. Many patients complain of a change in their sense of taste, and food becomes tasteless and often repulsive. Others become able to smell different odours that had been masked by anticholinergic drugs. This is not always an advantage, especially with hospital food! Changes in the colour of urine (first to a red tinge during voiding and then to black if it is left exposed to air) may frighten the patients, but these changes are only a biochemical marker of the presence of large amounts of L-dopa.

Biochemically, very few changes were noticed outside those related to catecholamines. Initially a slight increase in PBI was found in some cases, but with changes in the coating of the capsules this no longer occurred. Transient small increases in BUN were seen in 15 patients, but could be reversed by forcing fluids. More frequent were increases in uric acid (49% of patients) seen in an irregular manner. These increases were not dose-related and were quite variable. To date we have not been able to explain this finding, or to correlate it with any definite modification of symptoms. We did not observe hemolytic episodes or granulocytopenia, except transient minor decreases in total leukocyte counts in three patients. After L-dopa, urinary dopamine and homovanillic acid (HVA) levels, as well as HVA levels in CSF, increased to a marked degree, with a concomitant fall in 5 HIAA in the urine. These findings will be reported in more detail elsewhere.

L-DOPA IN OTHER DISEASES

We have tried L-dopa in six patients with other disorders of the central nervous system. The drug failed to produce any improvement in multiple sclerosis, senile dementia, dystonia musculorum deformans (one case) or Huntington's chorea (one case). One patient with a presenile dementia with some features of the Steele-Richardson-Olzewski syndrome was improved as far as his akinesia was concerned, but there were no changes in his mental functions. One patient with a purely akinetic form of luetic parkinsonism had a measurable improvement in akinesia of 35%.

Many authors have used L-dopa in other disease entities. Schildkraut *et al.*[98] in 1963, Klerman *et al.*[99] also in 1963, Friend, Bell and Kline[100] in 1965 and more recently Bunney *et al.*[97] in 1969 have reported some improvement in the retarded form of depression, but none in the agitated form. Gottfries, Gottfries and Roos[101] have indicated that levels of HVA are low in senile dementia, and it is therefore likely that some effect of L-dopa will eventually be observed in this condition, despite our negative findings in a single case.

At the 1969 meeting of the American Neurological Association, Coleman reported favourable effects in three patients with dystonia musculorum deformans. Good results had previously been obtained in spastic torticollis by Hirschmann and Mayer[102] in 1964 and by Pazzagli and Amaducci[103] in 1966. Wagshul and Daroff[104] obtained improvement in one patient with progressive supranuclear palsy, but failed to modify the symptoms in another. Similar negative results were reported by Gilbert and Feldman[105] and by Sacks.[106]

It would now appear that L-dopa may be useful in cases other than Parkinson's disease when there is a significant degree of akinesia. Otherwise little effect has been observed to date, except possibly in depression. There is therefore an important need for more studies in this field.

DOPA POTENTIATORS

Our own results, and those of most other groups, clearly indicate that L-dopa given in progressively higher oral doses, as recommended by Cotzias, is extremely useful in the symptomatic treatment of Parkinson's disease and in the extrapyramidal syndrome of manganese miners. However, peripheral and central side effects such as nausea, hypotension, abnormal involuntary movements and mental changes limit the long-term effectiveness of L-dopa, and so does the very high cost of this drug. It is obvious that new ways will have to be found to potentiate the antiparkinsonian effect of dopa, while reducing the unwanted complications.

Many years ago, some authors reported on the value of inhibitors of monoamine oxidase in alleviating some of the symptoms of Parkinson's disease.[20, 107, 108] Trials of this drug in conjunction with L-dopa, however, proved dangerous[17, 52, 109] because of hypertensive episodes and were soon abandoned.

Conventional anticholinergic therapy has been found by most authors to potentiate slightly the effect of L-dopa, particularly upon tremor.[94, 95] Recently, Schwab *et al.*[110] discovered some antiparkinsonian action in amantadine hydrochloride, a drug previously recommended for the prevention of certain strains of Asian influenza. Alone, amantadine appears to be more effective than the usual anticholinergic drugs and to predict the eventual benefit with L-dopa. In combination with the amino-acid, it is said to have a synergistic effect. If these results are confirmed by other groups, they will have great theoretical and possible therapeutic value.

In 1963, Pletscher and Gey[111] reported that a serylhydrazine derivative of trihydroxybenzyl, Ro 4-4602, inhibited at high doses (500 mg. per kg.) extra- and intracerebral dopa-decarboxylase, with a resulting drop in the concentrations of serotonin, dopamine and noradrenaline. Later the same group, with Bartholini, Burkard and Pletscher,[112] found that small doses (50 mg. per kg.) inhibited only peripheral decarboxylase, with a consequent increase in the intestinal absorption of L-dopa, increases in blood concentration of dopa and decreases in metabolites such as dopamine. The same inhibition of decarboxylase in brain capillaries, coupled with the high circulating concentrations of the precursor, resulted in an enhanced penetration of dopa within the brain, with subsequent metabolic degradation to dopamine. Ro 4-4602 (Hoffmann-La Roche) thus breaks down the blood-brain-barrier to L-dopa.

This principle was first applied to parkinsonian patients with favourable results by Birkmayer and Mentasti[113] from 1964 to 1967 and in 1969 by Tissot and collaborators[114] in Geneva, by Siegfried *et al.*[115] in Zürich, and by Barbeau and Gillo-Joffroy[116] in Montreal . Cotzias and Papavasiliou,[88] using alpha-methyl-dopa hydrazine, reported essentially similar results. In short, the combination of a peripheral decarboxylase inhibitor and L-dopa permitted reduction of the amino-acid dose to approximately 1 g. per day, with a reduction in the incidence of peripheral side effects (nausea, vomiting and hypotension) and with beneficial effects upon motor performance equal to those observed after at least 4 g. of L-dopa per day. Unfortunately the incidence of dyskinesias is as high as previously. To date the liver toxicity reported in dogs given extremely high doses of the drug have not occurred in humans after almost two years of continuous use of Ro 4-4602. However, one must be constantly aware of this potential danger. New, more potent decarboxylase inhibitors are now being prepared.

Among the many possible approaches that should be considered in the future are the following:

1. Preparation of slow-release capsules of dopa plus a decarboxylase-inhibitor combination.
2. Preparation of ether or ester derivatives of L-dopa.
3. Search for possible chemical analogues of both L-dopa and dopamine.
4. Search for substances, such as apomorphine, which may directly stimulate dopamine-sensitive receptors.

It is our opinion that L-dopa, as it is presently used (November 1969), cannot yet be marketed because of the cost, the cumbersome dosage schedule and the possible dangers of unsupervised usage. It is to be hoped, however, that a sufficient supply will be made available to qualified investigators, until such time as one of the other approaches mentioned above becomes practicable. We believe that L-dopa treatment of Parkinson's disease is only the first step to eventual success.

HOW DOES L-DOPA WORK?

We have reserved for the end a a difficult and obviously important question. The present approach to the treatment of Parkinson's disease may be the result of the most logical and direct chain of experiments in many years, but it is be-

coming increasingly evident that logic is not always right. At the low dosages used orally, or intravenously, until 1966, there is little doubt that the antiparkinsonian effect was due to the cerebral transformation of dopa into dopamine, particularly in the basal ganglia. The arguments for this have been thoroughly reviewed by Hornykiewicz.[15] The problem of site and mode of action, however, may be completely different with the large oral doses recommended by Cotzias since 1966. In this respect it should be mentioned that abnormal movements had not been observed with L-dopa previous to these new high levels.

It would now appear necessary to distinguish two types of effects of L-dopa:

1. A specific action by replenishing depleted dopamine stores in extrapyramidal centres and again stimulating specific dopamine receptors.

2. A non-specific action which may be mediated by dopa itself or its direct metabolites (3-methoxy dopa, for example) or abnormal accumulation of by-products (unusual methylated metabolites) upon the same centres, but more likely upon other areas where these substances are usually in low concentration (cortex, hypothalamus, brain stem). This non-specific action of L-dopa may also be carried out through the modification in amino-acid or amine contents of different parts of the brain brought about by the large intake of dopa.

It is obvious that recent observations in neuropharmacology and neurophysiology will have to be integrated with clinical observations to produce some understanding of the mode of action of dopa in Parkinson's disease and of the side effects observed. For example, it is probable that changes in other amines, most likely serotonin and tryptamine, produced either directly by large amounts of dopa or indirectly through some sort of balance system at the level of transport and uptake mechanisms, may be responsible for some of the psychiatric manifestations induced during therapy. Similarly a phenomenon of denervation hypersensitivity of dopamine receptors in the striatum may have to be invoked to explain some of the dyskinesias produced in parkinsonian patients with L-dopa, but not in normal control subjects or patients with other non-extrapyramidal types of CNS involvement.

Finally, it must be mentioned that dopa can produce some of its side effects through purely peripheral mechanisms. Recently we have demonstrated[117] that L-dopa will further reduce the already low plasma renin activity of akinetic parkinsonian patients and by this mechanism the complication of hypotension may possibly be explained. The role of dopamine in the postural control of blood pressure is presently under intensive study in our laboratory.

Résumé

Examen critique de neuf années d'expérience avec le traitement de la maladie de Parkinson par L-dopa

Les 10 dernières années furent fertiles en travaux concernant les catécholamines et plus particulièrement la dopamine. Le contenu très bas en dopamine des noyaux gris centraux et de l'urine chez les patients atteints de la maladie de Parkinson furent l'occasion logique d'essais cliniques de certains précurseurs tels la L-dopa. De 1961 à 1966, cette substance fut administrée par voie orale ou intraveineuse avec des résultats sur l'akinésie et la rigidité de plusieurs patients. Les doses employées étaient maintenues relativement basses à cause du coût de la drogue, les conclusions de ces essais furent controversées. L'introduction en 1966 de doses beaucoup plus élevées devait permettre d'observer un effet incontestable. Cependant en parallèle avec ces résultats prometteurs apparaissaient certains troubles secondaires tels l'hypotension et des mouvements anormaux et involontaires. Récemment de nouvelles approches ont été tentées pour résoudre ce problème. Le résultat net, toutefois, est de bouleverser nos concepts logiques, si bien établis, et de remettre en question plusieurs données expérimentales. Nous espérons qu'ainsi il sera possible de trouver une solution à cette angoissante maladie.

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REFERENCES

1. Schwab, R. S. and England, A. C.: Medical and surgical therapy of Parkinson's disease. *In*: Pathogenesis and treatment of parkinsonism, edited by W. S. Fields, Charles C Thomas Publisher, Springfield, 1958, p. 203.
2. Duvoisin, R. C.: *Bull. N.Y. Acad. Med.*, 41: 898, 1965.
3. Ehringer, N. and Hornykiewicz, O.: *Klin. Wschr.*, 38: 1236, 1960.
4. Barbeau, A.: *Neurology (Minneap.)*, 10: 446, 1960.
5. *Idem*: *A.M.A. Arch. Neurol.*, 4: 97, 1961.
6. Barbeau, A., Murphy, G. F. and Sourkes, T. L.: *Science*, 133: 1706, 1961.
7. Carlsson, A. *et al.*: *Ibid.*, 127: 471, 1958.
8. Carlsson, A.: *Pharmacol. Rev.*, 11: 490, 1959.
9. Everett, G. M. and Toman, J. E. P.: Mode of action of rauwolfia alkaloids and motor activity. *In*: Biological psychiatry, edited by H. J. Masserman, Grune & Stratton Inc., New York, 1959, p. 75.
10. Barbeau, A.: Biochemistry of Parkinson's disease. *In*: Proceedings of the seventh International Congress of Neurology, Rome, September 10-15, 1961, vol. 2, Societa Grafica Romana, Rome, 1961, p. 925.
11. Birkmayer, W. and Hornykiewicz, O.: *Wien. Klin. Wschr.*, 73: 787, 1961.
12. Bertler, A. and Rosengren, E.: *Acta Physiol. Scand.*, 47: 350, 1959.
13. Sano, I. *et al.*: *Biochim. Biophys. Acta*, 32: 586, 1959.
14. Blaschko, H.: *Experientia*, 13: 9, 1957.
15. Hornykiewicz, O.: *Pharmacol. Rev.*, 18: 925, 1966.
16. Bruno, A. and Cumer-Bruno, S.: *Riv. Neurobiol.*, 11: 813, 1965.
17. Barbeau, A.: *Canad. Med. Ass. J.*, 87: 802, 1962.
18. Barbeau, A. and Raymond-Tremblay, D.: Recent biochemical studies in Parkinson's disease and position of problem. *In*: Parkinson's disease, trends in research and treatment, a symposium held in Miami Beach, April 9-11, 1964, under the sponsorship of the National Parkinson Foundation, edited by A. Barbeau, L. J. Doshay and E. A. Spiegel, Grune & Stratton Inc., New York, 1965, p. 79.
19. Barbeau, A.: *Proc. Aust. Ass. Neurol.*, 5: 95, 1968.
20. van Praag, H. M.: *Psychiat. Neurol. Neurochir.*, 70: 361, 1967.
21. Bertler, A. and Rosengren, E.: *Pharmacol. Rev.*, 18: 769, 1966.

22. WEIL-MALHERBE, H. AND BONE, A. D.: *Nature (London)*, 180: 1050, 1957.
23. MONTAGU, K. A.: *Ibid.*, 180: 244, 1957.
24. MASUOKA, D. T., SCHOTT, H. F. AND PETRIELLO, L.: *J. Pharmacol. (Kyoto)*, 139: 73, 1963.
25. GLOWINSKI, J., IVERSEN, L. L. AND AXELROD, J.: *Pharmacologist*, 7: 156, 1965.
26. UDENFRIEND, S. AND CREVELING, C. R.: *J. Neurochem.*, 4: 350, 1959.
27. BOGDANSKI, D. F., WEISSBACH, H. AND UDENFRIEND, S.: *Ibid.*, 1: 272, 1957.
28. SHARMAN, D. F.: *J. Physiol. (London)*, 169: 950, 1963.
29. ANDEN, N. E., ROOS, B. E. AND WERDINIUS, B.: *Life Sci.*, 2: 448, 1963.
30. VOGT, M.: *Brit. Med. Bull.*, 21: 57, 1965.
31. ANDEN, N. E. *et al.*: *Life Sci.*, 3: 523, 1964.
32. DAHLSTRÖM, A. AND FUXE, K.: *Acta Physiol. Scand.*, 62 (Supp. 232): 1, 1964.
33. FUXE, K., HÖKFELT, T. AND NILSSON, O.: *Z. Zellforsch.*, 63: 701, 1964.
34. MCLENNAN, H.: *Experientia*, 21: 725, 1965.
35. POIRIER, L. J. AND SOURKES, T. L.: *Brain*, 88: 181, 1965.
36. GOLDSTEIN, M. *et al.*: *J. Neurochem.*, 16: 645, 1969.
37. POIRIER, L. J. *et al.*: *Brain Res.*, 14: 147, 1969.
38. MCLENNAN, H. AND YORK, D. H.: *J. Physiol. (London)*, 189: 393, 1967.
39. VAN ROSSUM, J. M.: *Arch. Int. Pharmacodyn.*, 160: 492, 1966.
40. GOLDBERG, L. I. *et al.*: Personal communication.
41. PLETSCHER, A., SHORE, P. A. AND BRODIE, B. B.: *J. Pharmacol. (Kyoto)*, 116: 46, 1956 (abstract).
42. CARLSSON, A., LINDQVIST, M. AND MAGNUSSON, T.: *Nature (London)*, 180: 1200, 1957.
43. PLETSCHER, A., BESENDORF, H. AND GEY, K. F.: *Science*, 129: 844, 1959.
44. CARLSSON, A. *et al.*: Effect of reserpine on the metabolism of catechol amines. *In*: Psychotropic drugs, edited by E. Garattini, N. V. Uitgevers. Mij., Elsevier, Amsterdam-C, 1957, p. 363.
45. DEGKWITZ, R. *et al.*: *Klin. Wschr.*, 38: 120, 1960.
46. BRUNO, A. AND CUMER-BRUNO, S.: *Acta Psychiat. Scand.*, 42: 264, 1966.
47. LAVERTY, R. AND SHARMAN, D. F.: *Brit. J. Pharmacol.*, 24: 759, 1965.
48. JUORIO, A. V., SHARMAN, D. F. AND TRAJKOV, T.: *Ibid.*, 26: 385, 1966.
49. SHARMAN, D. F.: *Ibid.*, 28: 153, 1966.
50. *Idem*: *Ibid.*, 30: 620, 1967.
51. DA PRADA, M. AND PLETSCHER, A.: *Experientia*, 22: 465, 1966.
52. BIRKMAYER, W. AND HORNYKIEWICZ, O.: *Arch. Psychiat. Nervenkr.*, 203: 560, 1962.
53. EVERETT, G. M. AND WIEGAND, R. G.: Pharmacology of catecholamines. *In*: Proceedings of the First International Pharmacological Meeting, Stockholm, 1961, vol. 8, Pharmacological analysis of central nervous action, edited by W. D. Paton, Pergamon Press Ltd., Oxford, 1963, p. 85.
54. SEIDEN, L. S. AND HANSON, L. C.: *Psychopharmacologia (Berlin)*, 6: 239, 1964.
55. BERNHEIMER, H. *et al.*: *Wiener Medizinische Akademie*, 4: 145, 1965.
56. HORNYKIEWICZ, O.: *Deutsch. Med. Wschr.*, 87: 1807, 1962.
57. BAROLIN, G. S., BERNHEIMER, H. AND HORNYKIEWICZ, O.: *Schweiz Arch. Neurol. Neurochir. Psychiat.*, 94: 241, 1964.
58. BERNHEIMER, H., BIRKMAYER, W. AND HORNYKIEWICZ, O.: *Klin. Wschr.*, 39: 1056, 1961.
59. HORNYKIEWICZ, O.: Metabolism of brain dopamine in human parkinsonism: neurochemical and clinical aspects. *In*: Biochemistry and pharmacology of the basal ganglia, edited by E. Costa, L. J. Côte and M. D. Yahr, Raven Press, Hewlett, N.Y., 1966, p. 171.
60. *Idem*: *Wien. Klin. Wschr.*, 75: 309, 1963.
61. BERNHEIMER, H. AND HORNYKIEWICZ, O.: *Naunyn Schmiedeberg Arch. Exp. Path.*, 247: 305, 1964 (abstract).
62. HORNYKIEWICZ, O.: *Ibid.*, 247: 304, 1964 (abstract).
63. BERNHEIMER, H., BIRKMAYER, W. AND HORNYKIEWICZ, O.: *Klin. Wschr.*, 41: 465, 1963.
64. BERNHEIMER, H. AND HORNYKIEWICZ, O.: *Naunyn Schmiedeberg Arch. Exp. Path.*, 243: 295, 1962 (abstract).
65. METZEL, E., WEINMANN, D. AND RIECHERT, T.: A study of the enzymes of dopa metabolism in parkinsonism from biopsies of basal ganglia. *In*: Third symposium on Parkinson's disease, edited by F. J. Gillingham and I. M. Donaldson, E. & S. Livingstone Ltd., Edinburgh, 1969, p. 41.
66. BERNHEIMER, H., BIRKMAYER, W. AND HORNYKIEWICZ, O.: *Wien. Klin. Wschr.*, 78: 417, 1966.
67. JOHANSSON, B. AND ROOS, B. E.: *Life Sci.*, 6: 1449, 1967.
68. GULDBERG, H. C. *et al.*: The use of cerebrospinal fluid in study of dopamine and 5-hydroxytryptamine metabolism in parkinsonism. *In*: Third symposium on Parkinson's disease, edited by F. J. Gillingham and I. M. Donaldson, E. & S. Livingstone, Ltd., Edinburgh, 1969, p. 50.
69. BISCHOFF, F. AND TORRES, A.: *Clin. Chem.*, 8: 370, 1962.
70. SOURKES, T. L.: *Progr. Brain Res.*, 8: 186, 1964.
71. WEIL-MALHERBE, H. *et al.*: *Clin. Res.* In press.
72. RINNE, U. K. AND SONNINEN, V.: *Ann. Med. Intern. Fenn.*, 57: 105, 1968.
73. WESTLAKE, R. J. AND TEW, J. M.: *Neurology (Minneap.)*, 16: 619, 1966.
74. O'REILLY, S., LONCIN, M. AND COOKSEY, B.: *Ibid.*, 15: 980, 1965.
75. GREER, M. AND WILLIAMS, C. M.: *Ibid.*, 13: 73, 1963.
76. RINNE, U. K., LAITINEN, L. V. AND SONNINEN, V.: *Psychiat. Neurol. (Basel)*, 153: 345, 1967.
77. BARBEAU, A.: *Agressologie*, 9: 195, 1968.
78. NASHOLD, B. S. AND KIRSCHNER, N.: *Neurology (Minneap.)*, 13: 753, 1963.
79. BARBEAU, A. AND TROMBITAS, S.: The metabolism of tritium labelled dopamine in parkinsonian patients. *In*: Progress in neuro-genetics, edited by A. Barbeau and J. R. Brunette, Excerpta Medica Foundation Publishers, Amsterdam, 1969, p. 352.
80. BARBEAU, A., JASMIN, G. AND DUCHASTEL, Y.: *Neurology (Minneap.)*, 13: 56, 1963.
81. RESNICK, R. H. *et al.*: *Proc. Soc. Exp. Biol. Med.*, 110: 77, 1962.
82. BARBEAU, A. *et al.*: Paper presented at the 13th Annual Meeting of the American Academy of Neurology, Detroit, April 27-29, 1961.
83. BARBEAU, A.: *Un. Méd. Canada*, 98: 183, 1969.
84. MCGEER, P. L. *et al.*: *J. A. M. A.*, 177: 665, 1961.
85. RINALDI, F., MARGHERITA, G. AND DE DIVITUS, E.: *Ann. Fren. Scienze, Affini*, 78: 105, 1965.
86. FEHLING, C.: *Acta Neurol. Scand.*, 42: 367, 1966.
87. COTZIAS, G. C., VANWOERT, M. H. AND SCHIFFER, L. M.: *New Eng. J. Med.*, 276: 374, 1967.
88. COTZIAS, G. C. AND PAPAVASILIOU, P. S.: Therapeutic studies of parkinsonian patients; long-term effects of DL-DOPA and L-DOPA. *In*: Second International Congress of Neuro-Genetics and Neuro-Ophthalmology of the World Federation of Neurology, Montreal, September 17-22, 1967, Excerpta Medical International Congress Series No. 154, Amsterdam, 1967, p. 30 (abstract).
89. YAHR, M. D. *et al.*: *Trans. Amer. Neurol. Ass.*, 93: 56, 1968.
90. TIMBERLAKE, W. H., ZIEPER, I. AND SCHWAB, R. S.: Double-blind study of L-DOPA treatment of parkinsonism. *In*: The Fourth International Congress of Neurobiological Surgery, and the Ninth International Congress of Neurology, New York, September 20-27, 1969, Excerpta Medica International Congress Series No. 193, Amsterdam, 1969, p. 170 (abstract).
91. COTZIAS, G. C.: *New Eng. J. Med.*, 281: 272, 1969.
92. DERY, J. P. *et al.*: *Un. Méd. Canada*, 91: 842, 1962.
93. JOUBERT, M. AND BARBEAU, A.: *Ibid.*, 95: 531, 1966.
94. COTZIAS, G. C., PAPAVASILIOU, P. S. AND GELLENE, R.: *New Eng. J. Med.*, 280: 337, 1969.
95. YAHR, M. D. *et al.*: *Arch. Neurol. (Chicago)*, 21: 343, 1969.
96. MCDOWELL, F. *et al.*: The treatment of Parkinson's disease with dihydroxyphenylalanine. *In*: The Fourth International Congress of Neurobiological Surgery, and the Ninth International Congress of Neurology, New York, September 20-27, 1969, Excerpta Medica International Congress Series No. 193, Amsterdam, 1969, p. 170 (abstract).
97. BUNNEY, W. E. *et al.*: *Lancet*, 1: 885, 1969.
98. SCHILDKRAUT, J. J. *et al.*: *Ann. N.Y. Acad. Sci.*, 107: 1005, 1963.
99. KLERMAN, G. L. *et al.*: *J. Psychiat. Res.*, 1: 289, 1963.
100. FRIEND, D. G., BELL, W. R. AND KLINE, N. S.: *Clin. Pharmacol. Ther.*, 6: 362, 1965.
101. GOTTFRIES, C. G., GOTTFRIES, I. AND ROOS, B. E.: *J. Neurochem.*, 16: 1341, 1969.
102. HIRSCHMANN, J. AND MAYER, K.: *Deutsch. Med. Wschr.*, 89: 1877, 1964.
103. PAZZAGLI, A. AND AMADUCCI, L.: *Riv. Neurobiol.*, 12: 128, 1966.
104. WAGSHUL, A. AND DAROFF, R. B.: *Lancet*, 2: 105, 1969.
105. GILBERT, J. J. AND FELDMAN, R. G.: *Ibid.*, 2: 494, 1969.
106. SACKS, O. W.: *Ibid.*, 2: 591, 1969.
107. GERSTENBRAND, F. AND PROSENZ, P.: *Praxis*, 54: 1373, 1965.
108. BARBEAU, A. AND DUCHASTEL, Y.: *Canad. Psych. Ass. J.*, 7 (Suppl.): S-91, 1962.
109. BARBEAU, A., SOURKES, T. L. AND MURPHY, G. F.: Les catécholamines dans la maladie de Parkinson. *In*: Monoamines et système nerveux. Paper presented at a symposium held at the Clinique de Bel-Air, September 1-2, 1961, edited by J. De Ajuriaguerra, Georg & Cie, Genève, 1962, p. 247.
110. SCHWAB, R. S. *et al.*: *J. A. M. A.*, 208: 1168, 1969.
111. PLETSCHER, A. AND GEY, K. F.: *Biochem. Pharmacol.*, 12: 223, 1963.
112. BARTHOLINI, G., BURKARD, W. P. AND PLETSCHER, A.: *Nature (London)*, 215: 852, 1967.
113. BIRKMAYER, W. AND MENTASTI, M.: *Arch. Psychiat. Nervenkr.*, 210: 29, 1967.
114. TISSOT, R. *et al.*: *Presse Méd.*, 77: 619, 1969.
115. SIEGFRIED, J. *et al.*: The treatment of Parkinson's disease with L-DOPA combined with a decarboxylase inhibitor. *In*: The Fourth International Congress of Neurobiological Surgery, and the Ninth International Congress of Neurology, New York, September 20-27, 1969, Excerpta Medica International Congress Series No. 193, Amsterdam, 1969, p. 171 (abstract).
116. BARBEAU, A. AND GILLO-JOFFROY, L.: Treatment of Parkinson's disease with L-DOPA and Ro 4-4602. *In*: The Fourth International Congress of Neurobiological Surgery and the Ninth International Congress of Neurology, New York, September 20-27, 1969, Excerpta Medica International Congress Series No. 193, Amsterdam, 1969, p. 171 (abstract).
117. BARBEAU, A. *et al.*: *Science*, 165: 291, 1969.
118. BRUCK, H. *et al.*: *Acta Neuropath. (Berlin)*, 3: 638, 1964.
119. BARTLETT, M. F., ULSHAFER, P. R. AND BARBEAU, A.: A chemical investigation of the urinary bases in Parkinson's disease. *In*: Second International Congress of Neuro-Genetics and Neuro-Ophthalmology of the World Federation of Neurology, Montreal, September 17-22, 1967, Excerpta Medica International Congress Series No. 154, Amsterdam, 1967, p. 28 (abstract).
120. MONTPLAISIR, J. AND BARBEAU, A.: Serum tyrosine in Parkinson's disease. *In*: Second International Congress of Neuro-Genetics and Neuro-Ophthalmology of the World Federation of Neurology, Montreal, September 17-22, 1967, Excerpta Medica International Congress Series No. 154, Amsterdam, 1967, p. 28 (abstract).
121. BARBEAU, A.: Unpublished results 1969.
122. BARBEAU, A. *et al.*: *Rev. Canad. Biol.*, 22: 469, 1963.
123. KEUHL, F. A., VANDERHEUVEL, J. A. AND ORMOND, R. E.: The pink spot and Parkinson's disease. *In*: Second International Congress of Neuro-Genetics and Neuro-Ophthalmology of the World Federation of Neurology, Montreal, September 17-22, 1967, Excerpta Medica International Congress Series No. 154, Amsterdam, 1967, p. 36 (abstract).
124. BOULTON, A. A.: The pink spot in parkinsonism. *In*: Second International Congress of Neuro-Genetics and Neuro-Ophthalmology of the World Federation of Neurology, Montreal, September 17-22, 1967, Excerpta Medica International Congress Series No. 154, Amsterdam, 1967, p. 35 (abstract).